ADENOMATOUS POLYPOSIS COLI AND RETINOIC ACID REGULATE THE TRANSCRIPTION FACTOR RUNX3. , Robert T. Jones[1], Itrat Jafri[2], David A. Jones*[2] University of Michigan - Dearborn[1], Department of Natural Sciences, Dearborn, MI 48128, University of Utah[2], Huntsman Cancer Institute, Salt Lake City, UT 84112, USA, david.jones@hci.utah.edu

RUNX3 is a transcription factor that plays an important role in several important developmental processes. Recent evidence suggests a potentially important role for RUNX3 loss in colon tumor development. As loss of the tumor suppressor adenomatous polyposis coli (APC) initiates colon tumor development, we examined the relationship between APC loss and RUNX3 expression using zebrafish harboring homozygous mutations in APC. Since we have shown previously that APC promotes the synthesis of retinoic acid, we also determined the effect of retinoic acid on RUNX3 expression. Paradoxically, analysis of RUNX3 expression by Q-RT-PCR revealed a two-fold increase in 72 hpf zebrafish embryos harboring homozygous mutations in APC relative to age-matched wild type and heterozygous siblings. Since the major developmental defects seen in homozygous APC mutant zebrafish fish result from loss of retinoic acid, we also examined mutant treated with retinoic acid. Consistent with a role for retinoic acid downstream of APC loss, treatment of APC mutant embryos with RA suppressed the dysregulated expression of RUNX3. To examine this further, we also performed whole mount in situ hybridizations to determine the exact tissues expressing RUNX3 following loss of APC. This analysis revealed high levels of RUNX3 in anterior regions of the embryos include the head, brachial arches and pectoral fins. In contrast, we saw little increase of RUNX3 within the developing intestine, thereby, suggesting tissue-specific regulation of RUNX3 following loss of APC and retinoic acid. Our findings suggest an important new regulatory link between APC and RUNX3 that is mediated by retinoic acid. These findings invite further investigation into the consequence of RUNX3 misexpression on intestinal development and colon tumor formation.